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(54) Aerosols containing anti-inflammatory steroids

(57) A process by means of which an increase in the particle size of a micro-ground anti-inflammatory steroid in the aerosol propellent is prevented. The increase in the particle size is prevented at the suspending stage when the solubility of the steroid into the propellant is reduced by using a low temperature (5 to –40°C) and by initially mixing only a little quantity of the propellant with the steroid. If desired, the smallest and dissolved steroid particles can be removed by filtering. The particle size does not become larger even afterwards when the suspension is allowed to be stabilized for a sufficiently long time before the temperature is raised or the rest of the propellant is added.

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SPECIFICATION

Process for the preparation of a mixture of an anti-inflammatory steroid and a fluoro - chloro - hydrocarbon to be used as a propellant

The subject of the present invention is a process for the preparation of a mixture of an anti-inflammatory steroid, such as beclometasone dipropionate ground into a particle size smaller than 5 μm, and of a fluoro - chloro - hydrocarbon to be used as a propellant, such as trichlorofluoromethane or dichloro - difluoromethane. The process in accordance with the invention is characterized in that the detrimental increase in the particle size of the steroid is prevented by suspending the steroid at a temperature of about +5 . . . −40°C into a little quantity of the propellant, by stirring the mixture for at least 24 hours, and by adding the necessary quantity of the propellant during or after the stirring. The mixture is stirred preferably for 1 to 3 days. Moreover, if desired, it is possible to filter the portion of the steroid that has the smallest particle size and that has been dissolved, off the mixture.

In mixtures prepared by means of the process in accordance with the invention, increase in the size of the crystals does not take place during storage either. Therefore they are suitable for use in aerosol preparations intended to be administered into the respiratory canals, in which preparations the active agent must be sufficiently finely divided in order to be able to be carried right into the area of the little bronchi.

From the British Patent 1 429 184 it is known that beclometasone dipropionate or some other corticosteroids which have been ground into a particle size suitable for inhalation, e.g. 2 to 5 μm, in the fluorochlorohydrocarbons used as aerosol propellants form rather large crystals or crystal agglomerations, larger than 20 μm. Particles of such a large size are not carried deep enough into the lungs.

In the above patent publication, the observation is also stated that, when the produced large crystals are ground back into the desired smaller crystal size, the crystals no longer become larger to a substantial extent. It is on this observation that the process in accordance with the said patent for the preparation of steroids of a sufficiently stable crystal size is based. According to the process, the crystals are first allowed to grow freely, possibly by means of recrystallisation, whereupon they are ground, e.g., in a ball mill to the desired crystal size. It may be necessary to remove the propellant before grinding, in which case the steroid must, of course, be suspended again into the propellant after the grinding.

In the grinding of a crystalline material, a considerable part of the material may be converted into a higher-energy, amorphic state. The growth of the steroid particles in fluoro - chlorohydrocarbons will be mainly due to the circumstance that the higher-energy, amorphic material tends to be dissolved and recrystallised into a lower-energy, organized stable state. The dissolution is favoured by the small size of the particles.

In a stable suspension of a steroid and a fluoro - chlorohydrocarbon, medium has been adsorbed uniformly on the surface of the solid particles. A kind of a "solvate" has been formed which prevents a growth of the crystals via dissolution and recrystallisation (cf. Finnish Pat. 53.067).

According to the present invention, stable suspensions can be prepared without increasing the particle size so that the dissolution of the steroid is reduced essentially during the stirring step. The dissolution is reduced by working at a low temperature (about −10 to −30°C) and by first mixing the steroid into a little quantity of propellant (e.g., 1 to 10% of the whole quantity). Attempts are made to perform the moistening of the steroid as uniformly as possible in order that no concentration gradients could be formed in the mixture. After the stabilization stage propellant can be added without an increase in the particle size. If desired, dissolved steroid can be removed by filtering by means of a membrane filter, at which time, when dissolving and mixing, it is possible to work at a higher temperature (about +5 to −10°C).

The process in accordance with the invention is industrially highly usable. By its means it is possible to prepare suspensions suitable for aerosol preparations by one unit operation, stirring, without having to perform a possible dissolution and recrystallisation or grinding. Grinding is not a recommendable operation in this connection, because it — besides increasing the work — may convert part of the material into excessively small or high-energy, amorphic particles, which may cause new growth of crystals. Moreover, too small and light particles are not recommendable even therefore that they do not settle easily from the breathing air onto the surface of the lungs.

An aerosol product prepared by means of the process in accordance with the invention, described in example 1, was compared with a product prepared by means of a conventional process.

The reference product was prepared as follows: 1.05 grams of micro-ground beclometasone dipropionate was suspended into 403 grams of trichloro fluoromethane at +15°C, 0.12 g of oleic acid was added, and the mixture was stirred for 6 hours, the temperature being still +15°C. 4.04 grams of the suspension were dosed into a can and the can was closed by means of a dose valve. 10.36 grams of dichloro - difluoromethane was added into the can by means of pressure.

The distribution of the particle size was determined out of the products immediately on preparation as well as after 1, 3, 42, and 61 days. On the basis of the distribution of the particle size, an average particle size based on the weight was calculated for each sample.

The results of the comparative test are given in the following table.

	Average particle size/μm				
Days after filling of can	0	1	3	42	61
Product as per invention	1.3	2.6	2.3	2.2	2.4
Reference product	1.9	6.2	13.9	19.4	21.9

During a storage of 61 days, the particle size of the product in accordance with the invention was not increased substantially, whereas the particle size of

the reference product became about 10-fold.

The following examples illustrate the invention.

EXAMPLE 1

1.05 g beclometasone dipropionate was suspended into 40 g trichloro - fluoromethane at −25°C. The mix was stirred by means of a magnetic agitator at −25°C for 3 days. The suspension was mixed into 362.8 g of trichloro - fluoromethane that had been cooled to +5°C, 0.12 g oleic acid was added, and the mix was stirred for another 0.5 hours. 4.04 g of the suspension prepared in this way was dosed into a can, the can was closed by means of a dose valve, and through the valve, 10.36 g dichloro - difluoromethane was added by means of pressure.

EXAMPLE 2

1.05 g beclometasone dipropionate and 4.0 g trichloro - fluoromethane were mixed at −20°C. To the mixture, trichloro - fluoromethane that had been cooled to −20°C was added as small quantities so that during the first 6 hours 36.0 g were added, during the next 12 hours 160 g, and during the next 18 hours 202.8 g.

EXAMPLE 3

0.5 g beclometasone diproprionate was added to dichloro - difluoromethane of −35°C (about 20 grams). The mix was stirred for 2.5 days at −25°C in a tightly sealed pressure-proof vessel by means of a magnetic agitator. The dichloro - difluoromethane was evaporated off. 200 g trichloro - fluoromethane were added. The mix was stirred at the room temperature for 4 hours.

EXAMPLE 4

3.15 g beclometasone dipropionate was suspended at +5°C into 150 ml trichloro - fluoromethane, the mix was stirred for 1 hour, and 120 ml trichloro - fluoromethane was removed by filtering by means of a 0.45 μm Millipore filter, and a corresponding quantity of pure trichloro - fluoromethane was added. The stirring, filtering, and addition were repeated 3 times. After the last time stirring was continued for 36 hours, whereupon trichloro - fluoromethane was added ad 1200 g. The temperature was all the time +5°C.

CLAIMS

1. A process for the preparation of a mixture of an anti-inflammatory steroid, such as beclometasone dipropionate ground into a particle size smaller than 5 μm, and of a fluoro - chloro - hydrocarbon to be used as a propellant, such as trichlorofluoromethane or dichloro - difluoromethane, characterized in that the detrimental increase in the particle size of the steroid is prevented by suspending the steriod at a temperature of about +5 to −40°C into a little quantity of the propellant, by stirring the mixture for at least 24 hours, and by adding the necessary quantity of the propellant during or after the stirring.

2. A process as claimed in claim 1, characterized in that the mixture is stirred for 1 to 3 days and propellant is added during or after this period.

3. A process as claimed in claim 1 or 2, characterized in that the steriod is suspended into the propellant at a temperature of about −10°C to −40°C.

4. A process as claimed in claim 3, characterized in that the steriod is suspended into trichlorofluoromethane at a temperature of about −15 to −25°C.

5. A process as claimed in claim 3, characterized in that the steriod is suspended into dichloro - difluoromethane at a temperature of about −25 to −35°C.

6. A process as claimed in claim 1 or 2, characterized in that the suspension is filtered during the stirring stage by means of a membrane filter of 0.2 to 0.5 μm.

7. A process as claimed in claim 6, characterized in that the steriod is suspended into the propellant at a temperature of about +5 to −10°C.

8. A process as claimed in claim 7, characterized in that the steriod is suspended into the propellant at a temperature of about +5 to 0°C.

9. A process as claimed in any of claims 1 to 4, characterized in that the quantity of propellant to be used at the beginning for suspending is 1 to 10 per cent by weight out of the total quantity of propellant.

10. A process according to claim 1 substantially as herein described with reference to any one of the examples.

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(54) Title: AEROSOL FORMULATIONS

(57) Abstract

The replacement of chlorofluorohydrocarbon propellants in medical aerosols is of the utmost importance to the pharmaceutical industry. A number of formulations have been investigated. The present invention provides a medical aerosol formulation comprising a particular medicament, a fluorocarbon propellant and 6 to 25 % w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant. Cannisters suitable for delivering such a pharmaceutical formulation are also provided.

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AEROSOL FORMULATIONS

This invention relates to pharmaceutical formulations for inhalation aerosols. The Montreal Protocol on ozone depleting gases has made the reformulation of existing pharmaceutical aerosols for inhalation treatment containing chlorofluorohydrocarbon propellants, a matter of urgency for the pharmaceutical industry.

A number of hydrofluorocarbons (HFCs) have been the subject to toxicological testing and two in particular P134a (1,1,1,2-tetrafluoroethane) and P227 (1,1,1,2,3,3,3-heptafluoropropane) have been identified as safe for use in pharmaceutical aerosols.

A number of patent applications have been submitted in this field, the first being EP 372777, which discloses the use of four component mixtures, comprising a medicament, a surfactant, P134a and a co-solvent of higher polarity than the P134a, in the form of a solution or a suspension.

As inhalation aerosols are meant for administration to the lung, it has long been accepted that such formulations should contain as few ingredients as possible, to avoid putting unnecessary materials into the lung.

Historically, despite EP 372777, solution aerosols contained only medicament, propellant or propellant mixtures and, if necessary, co-solvent, usually ethanol, eg US 2868691. The use of a surfactant was normally unnecessary for solution aerosols. However, historically medicinal suspension aerosols have contained a surfactant eg US 3014844, as it was considered that the use of a surfactant was necessary to prevent agglomeration of particles, to prevent adhesion to the sides of the canister, and to aid valve lubrication and prevent valve sticking.

However it was disclosed in EP 616525 that it is possible to prepare medicament suspensions in a hydrofluorocarbon without the need for a surfactant, if a polar co-solvent was added. The normal co-solvent ethanol, has well established

physiological actions and being a pure absorbable liquid eliminates any possibility of residues remaining in the lung. Irritation or possible toxicity from the surfactant, many of which are mixtures of similar compounds, are avoided.

EP 616525 specifically limits the polar co-solvent level to 0.01 to 5% w/w and in particular states (page 3, line 55) that the preferred level is about 0.1% w/w.

According to a first aspect of the present invention there is provided a medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

According to a second aspect of the present invention there is provided a medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

According to a third aspect of the present invention there is provided a canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

It has now been surprisingly found that higher levels of alcohol have beneficial results. Levels of 6% or more of ethanol produce satisfactory suspensions, which do not agglomerate on standing, and on reshaking produce finely dispersed medicament. It is believed that the higher levels of alcohol reduce the degree of deposition on the inside of the can. This is a very desirable feature. In addition, the use of these larger percentages of ethanol enables a much cheaper production process.

Medicinal aerosols can be filled either with one dose of liquid containing all of the ingredients mixed together or by

a two dose process where the first dose contains the medicament and all other ingredients, including co-solvents, surfactants, if any, ancillary compounds eg flavours, if any, and some times some of the propellant followed by a second dose of pure propellant. This two dose fill has major cost advantages in that the volume of mix for a fixed number of cans is significantly smaller enabling the use of smaller mixing vessels. In particular, with the use of the new HFC propellants, which have lower boiling points than the old CFC propellants, the use of a one dose fill may involve the use of cooled pressurised vessels to prevent evaporation of the propellant gas during mixing and filling. With the new formulations with added extra co-solvent a first mix of just medicament suspended in the co-solvent can be used, followed by a second dose of pure propellant. This means that the propellant can be dosed directly from a holding tank into the can without any need to mix and store with the other ingredients. For example a mix weight of 1g of medicament and co-solvent can be followed by 7.5g of propellant. In this way the volume to be mixed is reduced from 8.5g to 1g. All the examples in EP 616525 are of laboratory scale, where the handling problems are much easier, but all the formulations described are such that it would not be practicable to fill in two doses without mixing the propellant, as is the case with the present disclosure.

The description of the filling method given on page 5 lines 2-13 indicates that only a one dose filling method is envisaged.

In all cases of the present invention the medicament consists of a particle size suitable for inhalation into the lung and will thus be less than 100 microns, desirably less than 20 microns and preferably in the range of 1-10 microns, normally with a mean particle size 1-5 microns.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant.

Appropriate medicaments may thus be selected from, for example, analgesics, eg codeine, dihydromophine, ergotamine, fentanyl or morphine; anginal preparations, eg diltiazem; antiallergics, eg cromoglycate, ketotifen or nedocromil; anti-infectives, eg cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, eg methapyrilene; anti-inflammatories, eg beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, eg noscapine; bronchodilators, eg ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tolubuterol, orciprenaline; diuretics, eg amiloride; anticholinergics, eg ipratropium, atropine or oxitropium; hormones, eg cortisone, hydrocortisone or prednisolone; xanthines, eg aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, eg insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (eg as alkali metal or amine salts or as acid addition salts) or as esters (eg lower alkyl esters) or as solvates (eg hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Preferred are those compounds which are also substantially insoluble in the co-solvent. Particularly preferred as medicament is salbutamol either as base or as a salt and especially salbutamol sulphate.

Co-solvents may be selected from polar alcohols and polyols, particularly C_2-C_6 aliphatic alcohols and polyols, such as propylene glycol, and preferably ethanol. Levels of co-solvent will be between 6% and 25% w/w of the total canister content, preferably between 10-15% w/w of canister content.

The propellant may be a hydrofluorocarbon, particularly P134a or P227. Other hydrofluorocarbons or hydrocarbons or aliphatic gases (eg Dimethylether) may be added to modify the

propellant characteristics as required.

The product is preferentially produced by weighing the active medicament and suspending it in the co-solvent. The appropriate amount of suspension is then dosed into the can, followed by a second dose of propellant or propellant mix. However, a one shot fill or any other equivalent method may be employed.

The normal medicinal product on the market has an actuator with spray orifice diameter of about 480 microns. However, with the larger percentages of ethanol envisaged in this invention, it is desirable that the co-solvent evaporates from the particles as rapidly as possible.

This is achieved by reducing the aperture to between 100-300 microns, which for the same dosage or drug, gives more rapid evaporation of the co-solvent. A particularly preferred embodiment of the invention is a combination of a level 10-15% co-solvent (normally ethanol) with a stem aperture of 150-250 microns.

The invention is further described by means of example but not in any limitative sense.

Example

Salbutamol Sulphate	0.03g
Ethanol	0.97g
Tetrafluoroethane (P134a)	7.5g

The salbutamol sulphate previously micronised to give over 90% of particles below 10 microns was weighed out and added to the ethanol. The suspension was mixed until is was smooth and uniform and then filled into the aerosol canister. The metering valve assembly was crimped (preferably vacuum crimped) on the canister and then the P134a was filled through the valve. The valve capacity is such as to deliver 100 micrograms of salbutamol, as salbutamol sulphate per actuation.

A particularly preferred use of such a canister is in a patient breath operated device rather than the normal hand

operated device. Such devices are available commercially such as those under the trade mark "Easi-Breathe".

Claims:

1. A medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

2. A medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

3. A formulation as claimed in claim 1 or claim 2, wherein the medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.

4. A formulation as claimed in claim 3, where the medicament is ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropandamine, pirbuterol, reproterol, rimiterol terbutaline, isoetharine, orciprenaline, salbutamol, salmeterol, sodium cromoglycate, fluticasone, beclomethasone or similar molecule and any physiologically acceptable salt, solvate or ester of such compound.

5. A formulation, as claimed in claims 1-3, where the medicament is a salt of salbutamol.

6. A formulation, as claimed in claims 1-3, where the medicament is a salt of formoterol (sometimes called eformoterol).

7. A formulation according to any of claims 1 to 5, wherein the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.

8. A formulation according to any of claims 1 to 5,

where the co-solvent level is 10-15%.

9. A formulation according to any of claims 1-5, wherein the polar co-solvent is ethanol.

10. A canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

11. A canister according to claim 9, fitted into an adaptor with an aperture of 100-300 microns.

12. A product according to claims 9 and 10 where the medicament is as per claim 4.

13. A product according to claims 9-11, where the medicament is a salt of salbutamol.

14. A product according to claims 9-11, where the medicament is a salt of formoterol.

15. A canister according to claims 9 and 10, which is actuated by a breath operated device.

16. A product according to claim 15, where the medicament is a salt of salbutamol.

17. A product according to claim 15, where the medicament is a salt of formoterol.

INTERNATIONAL SEARCH REPORT

Intern al Application No PCT/GB 97/01502

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/12

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 93/11 745 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-15. --	1-5, 7-10
A	WO, A, 93/11 743 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-21. --	1-5, 7-10
A	WO, A, 94/03 153 (GLAXO GROUP LIMITED) 17 February 1994 (17.02.94), abstract; claims 1-12. --	1-5, 7-10
A	WO, A, 94/13 262 (JAGER et al.) 23 June 1994 (23.06.94), abstract; claims 1-38,	1-5, 7-9

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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	especially claim 4.	

ANHANG — ANNEX — ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif à la demande de brevet international n°

PCT/GB 97/01502 SAE 162218

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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